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ORIGINAL CLINICAL ARTICLE

The prevalence of thoracolumbar kyphosis in achondroplasia: a systematic review

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Abstract
Purpose Thoracolumbar kyphosis (TLK) is described as a common presentation in children with achondroplasia. However, the prevalence and development of TLK are ill-defined, as well as its clinical implications. The goal of this study was to assess the existing evidence on the prevalence and development of TLK from the literature.
Methods A systematic literature review was performed in PubMed, EMBASE, and Thomson Reuters (ISI) Web of Knowledge. Articles were selected and evaluated with the Newcastle–Ottawa Scale in duplicate. Articles were included when the included patients were diagnosed with achondroplasia and the prevalence of TLK in this population was reported.
Results Seven studies were included. The prevalence of TLK varied between 50 and 100%, but the populations differed significantly. Also, the measurement method and definition of TLK was not given in any of the included studies. Two studies reported TLK in different age categories, but the development of TLK through age could not be inferred. Overall, the methodological quality was low.
Conclusions The prevalence rates of TLK in achondroplasia could not be assessed from the literature because the populations differed and the definition of TLK in the studies was not described. In future studies, this definition needs to be given and patients need to be assessed over a longer period of time, with repeated assessments.

Keywords Achondroplasia · Kyphosis · Systematic literature review · Developmental bone diseases

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Introduction

Achondroplasia was first described in 1878 [1] and is the most common form of human skeletal dysplasia, with an estimated frequency of between 1 in 15,000 and 1 in 40,000 live births [2]. The literal meaning of the word achondroplasia is "without cartilage formation". Patients with achondroplasia possess a mutation in the fibroblast growth factor receptor-3 (FGFR3) gene on the short arm of chromosome 4, which affects the maturation of chondrocytes in the growth plate [3]. The transmission of achondroplasia is by an autosomal dominant type inheritance, although 80–90% of the patients have new mutations [4].

Clearly recognizable features of achondroplasia are shortening of the arms and limbs. The skull exhibits the characteristic macrocephaly with frontal bossing, saddle-nose deformity, and also a narrow foramen magnum and a short clivus. There are several characteristics of the achondroplastic spine that make the spinal canal narrow throughout and increase the chance that there is compression on the spinal cord or the cauda equina. The pedicles are short, particularly in the thoracolumbar region, and there is a reduction of the interpediculate spacing of the lumbar vertebrae, which is progressively smaller in the caudal direction [5].

The literature claims that achondroplasia is characteristically accompanied by kyphosis at the thoracolumbar junction (TLK) [6]. In combination with the narrow spinal

canal, this kyphosis can easily result in compression of the medulla and/or the conus medullae. Achondroplastic children are claimed to be born with this kyphosis, but the natural history of TLK is unknown. Although the problem itself has been addressed several times in the literature, there is, to our knowledge, a very limited number of studies available that discuss TLK in achondroplasia.

There are several items which are relevant to explore: firstly, the criterium for TLK, i.e., what degree of kyphosis has to be present to identify the thoracolumbar junction as kyphotic, is interesting. Also, the measurement method used to measure TLK needs to be clarified. Furthermore, it is of interest as to the prevalence of TLK in young children, how TLK develops towards adulthood, and what percentage of TLK leads to clinical symptoms. Finally, the interventions performed in order to decompress the medulla, either accompanied by spondylodesis or not, are relevant.

All these questions start with knowledge on the prevalence of TLK in achondroplasia. Therefore, a systematic review was performed on the prevalence of TLK in achondroplasia.

Materials and methods

Search and selection

An online search in "PubMed", "EMBASE", and "Thomson Reuters (ISI) Web of Knowledge" was performed for all available articles published from 1975 up to and including July 2010. The complete search query was: ((achondroplasia OR achondroplastic) AND (thoracolumbar OR thoraco OR thoracal) AND (kyphosis OR kyphotic OR gibbus)), with a limit placed on "human" in the study category. The abstracts and, if necessary, the full-text versions of all hits were then printed and carefully reviewed by two reviewers (XX and XX) for suitability for the study. Articles were considered to be suitable for a full review if they described prevalence rates of TLK in achondroplasia. Each article and its relevant data were discussed between the two reviewers until they reached agreement. The references of the included studies were checked for additional studies.

Quality assessment

Two reviewers (XX and XX) assessed the quality of the studies using the Newcastle–Ottawa Quality Assessment Scale for cohort studies [7]. The Newcastle–Ottawa Scale (NOS) is a scoring list that awards 'stars' for adequate selection of patients in the cohort, adequate comparability of cohorts, and for adequate assessment of the outcome. The categories in the original scale were adapted to apply to this review. The categories and the individual items in these categories are described in Table 1.The maximum number of stars that can possibly be awarded is eight: four stars in the "Selection" category, one in the "Comparability" category, and three stars in the "Outcome" category.

Data extraction and analysis

Data were extracted by one reviewer (XX) and checked by a second reviewer (XX). We extracted the percentage of patients with achondroplasia who had TLK, distributed by age if available, as well as the method to measure TLK and the threshold used for the definition of TLK. Furthermore, the average size of TLK, the sample size, the included patient diagnoses or selection methods, average age, and any spinal interventions were noted. The objective was to perform a meta-analysis in order to calculate the average prevalence of TLK in achondroplasia. Secondary anticipated analyses were the prevalence and extent of TLK in different age groups. However, due to insufficient comparable studies, only a descriptive analysis was feasible.

Results

A total of 42 publications were identified by the combined database search. After reviewing all articles, we initially selected 8 of the 42 articles which contained information on the prevalence of TLK in achondroplasia. One study was excluded because it investigated factors related to TLK in children with achondroplasia [8]. The authors included 48 out of 103 children with achondroplasia who met their inclusion criteria. Unfortunately, they did not describe what those criteria actually were and described the percentage improvement in TLK rather than the prevalence rates. The data of the remaining seven articles [9–15] were extracted from the publications and are summarized in Table 2.

Most studies were performed with limited subjects and none of the publications specified what was considered as TLK. Since the patient populations were fairly different, the numbers were difficult to compare and the aggregate would lead to an analysis of heterogeneous data. Therefore, we refrained from performing a meta-analysis and present only a descriptive analysis of the results.

Quality assessment

The consensus rating and awarded stars according to the NOS scale are summarized in Table 3. Most articles score low, between one and four stars, on the NOS scale. Across studies, all quality items scored low, there were no items which were over- or underrepresented. The publication with the most information on TLK, and development over time, deserved only one out of the possible eight stars [12].

Table 1 Newcastle–Ottawa Scale for the assessment of methodological quality

Category	Item	Explanation	Scoring	Star items
Selection	1) Representativeness	Is the study population representative for the average achondroplast in the community?	A) Truly representative	*
			B) Somewhat representative	*
			C) Selected group	
			D) No description	
	2) Controls	Are the subjects of the non-exposed control group from the same community as the exposed group?	A) From the same community	*
			B) From a different source	
			C) No description	
			D) No control group	
	3) Ascertainment of exposure	What methods were used to determine TLK?	A) Secure record	*
			B) Structured interview	*
			C) Written self-report	
			D) No description	
	4) Baseline	Is there a baseline measurement of TLK? Demonstration of to what extent TLK was present at start of the study	A) Yes	*
			B) No	
Comparability	1) Comparability	Study controls for TLK?	A) Yes	*
			B) No	
			C) No control group	
Outcome	1) Assessment of TLK	How was TLK assessed?	A) Blind assessment	*
			B) Record linkage	*
			C) Self-report	
			D) No description	
	2) Follow-up	The development of TLK over a longer period, i.e., from birth, early childhood to adolescence, and mature bone	A) Yes	*
			B) No	
	3) Attrition	Adequate follow-up	A) Complete follow-up	*
			B) Less than 20% lost	*
			C) More than 20% lost	
			D) No statement	

Discussion

This study demonstrates that there is very little information available on the prevalence of thoracolumbar kyphosis in achondroplasia. For those studies that represent prevalence rates, it is unclear if these numbers are reliable estimates. Moreover, none of the articles retrieved provided a definition of TLK. The majority of articles did provide some information on the degree of kyphosis in symptomatic patients, but none included data on controls. In order to judge TLK in an achondroplasia patient and to consider treatment, it is obligatory to be informed of the reference data. These are simply lacking in the literature. One could argue, however, that any angle present in the thoracolumbar junction may be regarded upon as pathological, since this junction should be straight, without kyphosis.

The phenomenon of TLK is frequently mentioned in the literature on achondroplasia, and is often addressed as being a potentially serious problem [4]. For that reason, it is remarkable that there are few studies available reporting on the prevalence and follow-up of TLK and the average size of TLK in achondroplasia. More so, the sample sizes of the reported studies are too low to establish a stable estimate of the prevalence.

Kopits [12] is the only publication that specifically produced prevalence rates of TLK in several age groups. It, nevertheless, scored the lowest on the NOS scale. The article contains graphs and tables with a clear age distribution of the prevalence of TLK in achondroplasia and included more subjects than all patients from the other studies combined. The article is, however, descriptive and does not compare controls with patients, and neither does it compare treated with untreated patients. A protocol was introduced that prescribes a thoracolumbar brace to young children (aged 8 months to 2 years) to redress the TLK. To what extent the results of the treatment according to the protocol influences the prevalence rates of TLK in the different age groups is not clear.

Table 2 Characteristics of the included studies

Article	*N*	Patient population	TLK prevalence	TLK criterium	Average TLK (°)	Distribution by age	Average age (years)
Sciubba et al. [15]	44	Preoperative pediatric patients undergoing spinal decompressive procedures	50% (22)	Unknown	Unknown	Unknown	12.7 (range 5–21)
Schkrohowsky et al. [14]	44	22 with spinal stenosis (SS), 22 without SS	100% (44)	Unknown	With SS: 24.2 (range 11.7–36.7) Without SS: 14.1 (range 4.5–23.7)	Unknown	With SS: 11.1 (range 6.9–15.3) Without SS: 11.5 (range 7.7–15.3)
Ain et al. [9]	10	Laminectomy patients	100% (10)	Unknown	Preoperative: 63 (range 46–101) Postoperative: 94 (range 78–135)	Unknown	9.2 (range 6–16)
Savini et al. [13]	8	Surgery patients, kind of surgery not specified	100% (8)	Unknown	56 (range 18–89)	Unknown	37 (range 8–55)
Kahanovitz et al. [11]	36	Hospital database	50% (18)	Unknown	38 (range 14–110)	Unknown	15 and older
Bethem et al. [10]	30	Hospital database	60% (18)	Unknown	<50–132 (no average mentioned)	<4 years: 50% >4 years: 50%	0–60 (no average mentioned)
Kopits [12]	197	Unknown	53% (104)	Unknown	Unknown	<1 years: 94% 1–2 years: 87% 2–5 years: 39% 5–10 years: 11% 10–15 years: 20% 20–50 years: 35%	8.7 (range 1 month–76 years)

Table 3 Results of the quality assessment for the included studies

	Sciubba et al. [15]	Schkrohowsky et al. [14]	Ain et al. [9]	Savini et al. [13]	Kahanovitz et al. [11]	Bethem et al. [10]	Kopits [12]
Selection							
Representativeness	C	C	C	C	B (*)	B (*)	D
Selection of non-exposed cohort	D	D	D	D	D	A (*)	A (*)
Ascertainment of exposure	D	A (*)	A (*)	D	D	D	D
Baseline measurement	A (*)	A (*)	A (*)	A (*)	B	B	B
Comparability							
Comparability	C	C	C	C	C	A (*)	C
Outcome							
Assessment of outcome	D	D	A (*)	D	D	D	D
Follow-up	B	B	B	A (*)	B	A (*)	B
Follow-up adequacy	A (*)	A (*)	A (*)	A (*)	C	C	D

Another important issue is the development of TLK over time. Only two studies [10, 12] reported on TLK in different age categories, but these studies were not longitudinal studies, so development within patients cannot be ascertained with these designs. Kopits [12] suggests that TLK is widely distributed amongst newborns and that, over time, TLK diminishes. It would be interesting to know whether this is true and whether the persistence of TLK is related to clinical symptoms, but like data on the prevalence, these data are not available.

Most articles scored low on the adapted NOS. To gain points on this scale, the study population needed to be representative for the general achondroplasia population. Only two studies [10, 11] score a star for representativeness, under the assumption that hospital databases are a fairly complete source of achondroplasia patients. The patients described in the other articles [9, 13–15] are subjects selected from surgery cohorts, thus, suffering from clinical symptoms with an indication for surgery. Moreover, no controls were described, no definition of TLK was given, and no follow-up of patients was reported.

Our search resulted in a relatively low number of hits. This might be explained by the total number of publications related to achondroplasia, which is limited. We checked the references of the included studies to verify that no publications were missed.

In conclusion, there is no publication available that produces evidence-based prevalence rates of TLK in achondroplasia. The first step would be to define TLK and to investigate the prevalence of TLK. Therefore, we have initiated a study to produce a definition for and discover the prevalence rates of TLK in achondroplasia, preferentially distributed by age. If these data were to be available, the next step would be to investigate the development of TLK over time and to establish what percentage of achondroplasia with TLK has clinical symptoms. Finally, these data could help in making decisions on the surgical interventions needed.

References

1. Parrot J (1878) Sur la malformation achondroplastique et le Diu Ptauh. Bull Soc Anthrop 1:296–308
2. Francomano CA (1995) The genetic basis of dwarfism. N Engl J Med 332:58–59
3. Bonaventure J, Rousseau F, Legeai-Mallet L, Le Merrer M, Munnich A, Maroteaux P (1996) Common mutations in the fibroblast growth factor receptor 3 (FGFR 3) gene account for achondroplasia, hypochondroplasia, and thanatophoric dwarfism. Am J Med Genet 63:148–154
4. Horton WA, Hall JG, Hecht JT (2007) Achondroplasia. Lancet 370:162–172
5. Srikumaran U, Woodard EJ, Leet AI, Rigamonti D, Sponseller PD, Ain MC (2007) Pedicle and spinal canal parameters of the lower thoracic and lumbar vertebrae in the achondroplast population. Spine (Phila Pa 1976) 32(22):2423–2431
6. Kopits SE (1988) Orthopedic aspects of achondroplasia in children. Basic Life Sci 48:189–197
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P (2010) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available online at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 1 October 2010
8. Borkhuu B, Nagaraju DK, Chan G, Holmes L Jr, Mackenzie WG (2009) Factors related to progression of thoracolumbar kyphosis in children with achondroplasia: a retrospective cohort study of forty-eight children treated in a comprehensive orthopaedic center. Spine (Phila Pa 1976) 34(16):1699–1705
9. Ain MC, Shirley ED, Pirouzmanesh A, Hariri A, Carson BS (2006) Postlaminectomy kyphosis in the skeletally immature achondroplast. Spine (Phila Pa 1976) 31(2):197–201
10. Bethem D, Winter RB, Lutter L, Moe JH, Bradford DS, Lonstein JE, Langer LO (1981) Spinal disorders of dwarfism. Review of the literature and report of eighty cases. J Bone Joint Surg Am 63(9):1412–1425
11. Kahanovitz N, Rimoin DL, Sillence DO (1982) The clinical spectrum of lumbar spine disease in achondroplasia. Spine (Phila Pa 1976) 7(2):137–140
12. Kopits SE (1988) Thoracolumbar kyphosis and lumbosacral hyperlordosis in achondroplastic children. Basic Life Sci 48:241–255
13. Savini R, Gargiulo G, Cervellati S, Di Silvestre M (1991) Achondroplasia and lumbar spinal stenosis. Ital J Orthop Traumatol 17(2):199–209
14. Schkrohowsky JG, Hoernschemeyer DG, Carson BS, Ain MC (2007) Early presentation of spinal stenosis in achondroplasia. J Pediatr Orthop 27(2):119–122
15. Sciubba DM, Noggle JC, Marupudi NI, Bagley CA, Bookland MJ, Carson BS Sr, Ain MC, Jallo GI (2007) Spinal stenosis surgery in pediatric patients with achondroplasia. J Neurosurg 106:372–378